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How best to improve survival in hemodialysis patients: solute clearance or volume control?

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How much dialysis is required for optimal well-being and long-term survival? The Frequent Hemodialysis Network completed two prospective trials examining the effect of more frequent, short hours and, now, of nocturnal hemodialysis compared with standard thrice-weekly treatments. Whereas the short-hours trial reported benefits with more frequent dialysis, somewhat paradoxically, nocturnal hemodialysis had fewer advantages. However, this trial was probably underpowered, and confounded by the beneficial effects of home hemodialysis in the control group.

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The paradigm of hemodialysis has evolved from a life-saving treatment for a minority of patients with acute kidney injury to a life-sustaining therapy for many thousands of patients with chronic kidney disease stage 5 worldwide. Although hemodialysis treatments have become established as part of routine medical practice, moving out from specialized academic centers to free-standing satellite dialysis centers and to the patient's home, survival remains disappointing, with 5-year UK survival rates around 46%, compared with 44% for ovarian cancer, and 54% for colonic cancer. In addition, hemodialysis is expensive, consuming 2–3% of the overall UK health-care budget despite treating only 0.04% of the population.

As the survival of kidney transplant patients and those with stable chronic kidney disease stages 3–4 is greater than that of hemodialysis patients, it has been argued for many years that the amount of endogenous renal function or renal replacement therapy affects survival. The National Cooperative Dialysis Study, the first randomized controlled study of dialysis dose, used an assessment of urea clearance corrected for body water (Kt/V_{urea}) and defined a sessional 'adequacy' threshold for thrice-weekly hemodialysis of 0.9, below which complication-free survival was compromised within months.[1] Later observational studies suggested that higher sessional doses were associated with improved outcomes, and by consensus the sessional Kt/V_{urea} target was raised to 1.2.[2] A second randomized controlled study, the HEMO Study, demonstrated that targeting doses to a sessional Kt/V_{urea} of 1.45 did not appear to improve survival further,[3] although subgroup analysis suggested women may benefit from higher Kt/V_{urea} doses, fueling suggestions that prescribing dialysis to achieve Kt/V_{urea} targets may lead to underdosing of women and small men.[4] Observational studies typically based on home-hemodialysis cohorts or single centers reported improved survival of patients treated with more frequent hemodialysis and extended hours of hemodialysis.[5] As these studies were confounded by patient selection bias, the Frequent Hemodialysis Network (FHN) Trial Group organized two prospective randomized trials to study the effect of increasing the dose of standard thrice-weekly dialysis, by increasing dialysis frequency. The first study examined the effect of six short weekly hemodialysis sessions, averaging 154 min, in 125 patients, compared with thrice-weekly dialysis for an average of 213 min in 120 patients, delivering an average weekly standard Kt/V_{urea}, adjusted for session duration and frequency, of 3.6 compared with 2.57 (40% average increase), although the average weekly dialysis time was increased by only 22% (12.7 vs. 10.4 h, respectively).[6] This relatively greater increase in Kt/V_{urea} is due to the higher urea concentration gradient during the early phase of the dialysis session (Figure 1). This study lasted 12 months, and there was no difference in patient survival; however, two predetermined co-primary end points—mortality or increase in left ventricular mass, and mortality or decrease in physical health composite score—were significantly lower in the more frequent hemodialysis group. The second study (Rocco *et al.*,[7] this issue) planned to examine the effect of both increased frequency and duration of sessions, by recruiting 250 patients randomized to six in-center nocturnal dialysis sessions with standard thrice-weekly dialysis. However, only 87 were recruited, who then had unsupervised home hemodialysis, reducing the power of the study.[7] Despite a greater dose of Kt/V_{urea} delivered with more frequent nocturnal dialysis (mean 5 vs. 2.9 sessions per week, average session 379 vs. 256 min, 30.8 vs. 12.6 h hemodialysis/week, weekly standard Kt/V 5.0 vs. 2.9), and greater phosphate removal, there was no difference in 1-year mortality, or in the same two co-primary end points used in the FHN shorter-hours study. Although the nocturnal study was most likely underpowered, and confounded by improvements in the control group from switching to home hemodialysis. In addition, greater delivered Kt/V_{urea} did not improve cognitive performance, self-reported depression, or serum albumin or reduce erythropoietin requirements in either trial.

Although the amount of dialysis delivered is assessed in terms of urea clearance, urea is only one of many metabolites that accumulate in chronic kidney disease stage 5, and there has been renewed interest in other azotemic toxins. As the role and importance of individual toxins

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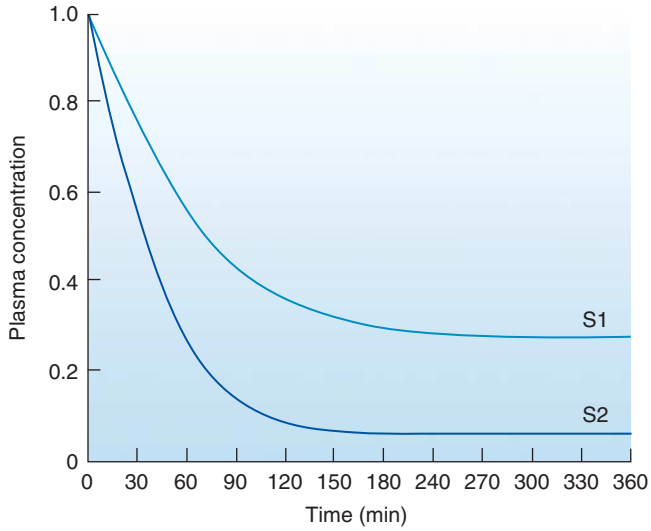

Figure 1 | Solute kinetics in hemodialysis. Change in plasma concentration of solute 1 (S1), which readily moves from intracellular compartment to plasma, such as urea, and solute 2 (S2), which moves slowly from intracellular compartment to plasma, such as a middle molecule or protein-bound toxin.

remain to be elucidated, β_2-microglobulin has often been used as a surrogate for middle-sized molecular azotemic toxins. The HEMO Study reported an increased risk of death with increasing serum β_2-microglobulin concentrations,[8] but was unable to demonstrate an overall survival benefit with high-flux membranes, with greater removal, middle molecule including β_2-microglobulin. However, subgroup analysis suggested that high-flux membranes conferred a survival advantage for prevalent patients established on dialysis for more than 3.6 years.[3] The Membrane Permeability Outcome study also failed to show an overall survival benefit of high-flux membranes, but there was a survival advantage for high-risk patients.[9] The FHN Trial Group used high-flux dialyzers for both groups. However, as diffusive clearance depends on size and free plasma water concentration, clearance of middle molecules is predominantly limited by dialysis-session time, and removal of β_2-microglobulin and protein-bound toxins would have been greater in the more-frequent nocturnal group. Indeed, phosphate removal was so effective in the nocturnal group that dialysate phosphate supplementation was required. So why was there no improvement in mortality, or in cognitive performance, self-reported depression, or serum albumin, and no reduction in erythropoietin-stimulating agents? This was a 12-month study, and accumulation and toxicity of azotemic middle molecules probably takes years; and some 25% of subjects dialyzed fewer than five times per week. In addition, only 87% completed the study, and many had dialyzed for less than 12 months and so retained residual renal function.

Removal of azotemic middle molecules can be further increased by the addition of convection, and studies of hemodiafiltration have reported lower serum β_2-microglobulin and phosphate levels in comparison with high-flux hemodialysis.[10] The question of whether these surrogates based on improved middle-molecule removal translate into improved patient survival led to a number of prospective multicenter trials. Some of these trials have now been completed and are expected to report shortly. If these trials show a survival benefit for hemodiafiltration, then this will support a role for the toxicity of azotemic middle molecules. Although some of these putative toxins, such as serum β_2-microglobulin, can be removed by hemodiafiltration and free light chains by high-permeability dialyzer membranes, removal of protein-bound azotemic toxins is typically limited by the equilibrium rate between free and protein-bound forms.

Although much attention has centered on small- and middle-molecule removal, dialysis is much more than simply urea clearance. Dialysis treatments are equally prescribed to achieve homeostasis, by correcting volume overload, sodium balance, and metabolic acidosis and maintaining divalent ion balance. The advent of multi-frequency bioimpedance devices and biomarkers of volume overload has shown that many hemodialysis patients fail to achieve adequate volume control and remain permanently volume overloaded throughout the dialysis week. Many patients with chronic kidney disease stage 5 entering hemodialysis programs have hypertension, left ventricular hypertrophy, and abnormal pulse-wave velocity. Not surprisingly, cardiovascular mortality remains the major cause of death of hemodialysis patients. One major advantage of more frequent hemodialysis is that shorter interdialysis intervals lead to reduced intradialytic weight gains. Thus the more frequent daily dialysis and nocturnal FHN groups had lower total ultrafiltration and ultrafiltration requirements per treatment session, resulting in a lower frequency of intradialytic hypotension.

In addition, not only did blood pressure control improve during the 12-month studies in both more frequent dialysis groups, but patients also required fewer antihypertensive medications. Echocardiography and pulse-wave velocity are affected by volume status, such that assessments of left ventricular mass differ depending on whether echocardiography is performed before, after, or on the non-dialysis day. The FHN studies measured left ventricular mass with magnetic resonance imaging, which is less affected by volume status. Left ventricular mass was significantly reduced only in the more frequent daily dialysis study and not in the nocturnal home hemodialysis study. Although there may be many possible explanations, in the more frequent dialysis study, the average standard dialysis-session time for the thrice-weekly treatment groups was only 213 min, compared with 256 min in the home hemodialysis study. Therefore, it is most likely that those patients treated with shorter session times failed to achieve adequate sodium removal and were more likely to be volume overloaded during the dialysis week. Thus, differences in volume status may partially explain the different

study findings. In the smaller, nocturnal study the greater amount of dialysis delivered in the standard-treatment arm may have reduced differences in volume status due to the fact that 25% of nocturnal patients dialyzed fewer than five times per week.

Although more frequent treatments were advantageous in terms of blood pressure control and reduced intradialytic hypotension and phosphate control, were there any adverse effects? In both studies there were an increased number of access interventions, particularly with fistulae in the nocturnal hemodialysis group. This experience differed from those in observational reports of more frequent dialysis and requires explanation. Unfortunately, the reasons for access interventions were not elucidated, and whether this related to the type of access and needling technique was not specified. Thus, although there are advantages to more frequent dialysis, more frequent needling may potentially lead to more access interventions.

DISCLOSURE

The author declared no competing interests.

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